SEQUENCE LISTING



<110>	Mahanthappa,	Nagesh	Κ.
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<120> NEUROPROTECTIVE METHODS AND REAGENTS

<130> ONV-043.02

<140> 09/418,221

<141> 1999-10-14

<150> 08/883,656

<151> 1997-06-27

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<170> PatentIn Ver. 2.0

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tgc gct ctt tta gtc tcc tct ggg ctg act tgt gga cca ggc agg ggc 96
Cys Ala Leu Leu Val Ser Ser Gly Leu Thr Cys Gly Pro Gly Arg Gly
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att gga aaa agg agg cac ccc aaa aag ctg acc ccg tta gcc tat aag 144
Ile Gly Lys Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys
35 40 45

cag ttt att ccc aat gtg gca gag aag acc cta ggg gcc agt gga aga 192 Gln Phe Ile Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Arg 50 55 60

tat gaa ggg aag atc aca aga aac tcc gag aga ttt aaa gaa cta acc
Tyr Glu Gly Lys Ile Thr Arg Asn Ser Glu Arg Phe Lys Glu Leu Thr
65 70 75 80

cca aat tac aac cct gac att att ttt aag gat gaa gag aac acg gga 288 Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Gly 85 90 95

gct gac aga ctg atg act cag cgc tgc aag gac aag ctg aat gcc ctg 336 Ala Asp Arg Leu Met Thr Gln Arg Cys. Lys Asp Lys Leu Asn Ala Leu 100 105 110

														gtg Val		384
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		_						_					_	aca Thr		624
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_	_		_	_	_	_		_			_			agt Ser	_	720
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_			_		_			_		_		_	_	gcg Ala	_	816
	_				_		_							aca Thr		864
														ggc Gly		912
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ctc acc gcc cag ggc acc atc ctc atc aac cgg gtg ttg gcc tcc t Leu Thr Ala Gln Gly Thr Ile Leu Ile Asn Arg Val Leu Ala Ser C 340 345 350	
tac gcc gtc atc gag gag cac agt tgg gcc cat tgg gcc ttc gca c Tyr Ala Val Ile Glu Glu His Ser Trp Ala His Trp Ala Phe Ala E 355 360 365	
ttc cgc ttg gct cag ggg ctg ctg gcc gcc ctc tgc cca gat ggg g Phe Arg Leu Ala Gln Gly Leu Leu Ala Ala Leu Cys Pro Asp Gly A 370 375 380	-
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	_		_			_	_	_				gaa Glu		432
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		_				_	_	-	_			tca Ser		576
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	_		_	 _		_		_		_		gac Asp		672
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												gct Ala 255		768
				_	_		_	_				cat His	_	816
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ggg gac gcg ctc Gly Asp Ala Leu 305				
gcc gtg ggc gtg Ala Val Gly Val		o Leu Thr A		
aac gac gtc ctc Asn Asp Val Leu 340			 	
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						ccc Pro										288
_		_	_	_		atg Met		_	_	_	_	_	_	_		336
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	_			_	_	gcg Ala	_		_			_			_	528
						aag Lys	_				_		_	_		576
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	_		_			ctg Leu	_	_		_	_	_	_	_	_ ~	768
	_	_				cag Gln	_		_	_		_			_	816
						att Ile										864
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ctg gta tca g Leu Val Ser (305	Gly Val										960
tcc acc cac o											1008
aca ctt gtg o				Ser							1056
gac cac cat o Asp His His I 355			_			_	_	_			1104
agt ttg gca t Ser Leu Ala 7 370				_			_				1152
cct cag atg o P <u>ro Gln M</u> et I 385	Leu Tyr										1200
ttc cat cca c Phe His Pro I						tgaa	ıggga	act o	ctaac	ccactg	1253
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Met Leu Leu I 1 ctg ctg gtg t	Leu Leu 5 tgc ccc Cys Pro 20 cac ccc	Ala Arg ggg ctg Gly Leu aaa aag	gcc tgt Ala Cys ctg acc	Leu 10 ggg Gly	Val ccc Pro	ggc Gly	Leu agg Arg	Ala ggg Gly 30 aag	Ser 15 ttt Phe cag	Ser gga Gly ttt	

											acc Thr			240
			_			_	_	 -		_	gga Gly	_	_	288
											ttg Leu 110			336
											acc Thr			384
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_	-		_								aag Lys			480
_	_	_	_	_	_	 _	_				gtc Val			528
_			_			_			_		aac Asn 190			576
											gtg Val			624
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											gac Asp	_		720
											tac Tyr			768
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gcg ctc ttt Ala Leu Phe 290			Arg							912
gct gaa cgc Ala Glu Arg 305										960
gtg acg ctg Val Thr Leu										1008
cac ggc acc His Gly Thr					_	_	_	_	_	1056
atc gag gag Ile Glu Glu 355	_			 _				_	_	1104
gcg cac gcg Ala His Ala 370			Leu							1152
ggc ggg ggc Gly Gly Gly 385										1200
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													atc Ile		336
									-				ggc Gly		384
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													tac Tyr 175		528
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					_			 _	_	_	_	_	ctc Leu	_	624
													aag Lys		672
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_		_		_	_	aag Lys					_	_				816
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						cca Pro	-								_	1008
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gcc aaa tcg gga ggc tgc ttc ccg ggc tcg gcc acg gtg cac ctg gag

Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Ala Thr Val His Leu Glu

205

200

195

624

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Gln Phe Ser Pro	Asn Val Pro		Leu Gly Ala Ser Gly Arg	248								
	Ile Ala Arg		cgc ttc aag gag ctc acc Arg Phe Lys Glu Leu Thr 80	296								
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			cac His					488
			acc Thr					536
			gca Ala 170				gtg Val	584
			gtg Val					632
			ggc <u>Gl</u> y					680
			gtg Val					728
			gag Glu					776
			gag Glu 250					824
			cca Pro					872
			aat Asn					920
			gtg Val					968
			cct Pro					1016
			gcc Ala 330					1064

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cac ctg gct cag ttg gcc ttc tgg ccc ctg aga ctc ttt cac agc ttg His Leu Ala Gln Leu Ala Phe Trp Pro Leu Arg Leu Phe His Ser Leu 355 360 365 370	1160
gca tgg ggc agc tgg acc ccg ggg gag ggt gtg cat tgg tac ccc cag Ala Trp Gly Ser Trp Thr Pro Gly Glu Gly Val His Trp Tyr Pro Gln 375 380 385	1208
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agc ttg ctt ctg acg cct tgt gga tta gcc tgt ggt cct ggt aga ggt Ser Leu Leu Thr Pro Cys Gly Leu Ala Cys Gly Pro Gly Arg Gly 20 25 30	96
tat gga aaa cga aga cac cca aag aaa tta acc ccg ttg gct tac aag Tyr Gly Lys Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys 35 40 45	144

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	_									_				ctg Leu		240
														aca Thr 95		288
_	_		_	_		_	_	_	_	_	_			tcg Ser	_	336
_														gtc Val		384
														cac <u>Hi</u> s		432
			_		_					_		_		agc Ser	_	480
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														acg Thr		624
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														cgt Arg		384
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														gtg Val 255		768

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					gtc Val										912
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Ile Gly Lys Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys
35 40 45

Gln Phe Ile Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Arg
50 55 60

Tyr Glu Gly Lys Ile Thr Arg Asn Ser Glu Arg Phe Lys Glu Leu Thr 65 70 75 80

Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Gly 85 90 95

Ala Asp Arg Leu Met Thr Gln Arg Cys Lys Asp Lys Leu Asn Ala Leu 100 105 110

Ala Ile Ser Val Met Asn Gln Trp Pro Gly Val Lys Leu Arg Val Thr 115 120 125

Glu Gly Trp Asp Glu Asp Gly His His Ser Glu Glu Ser Leu His Tyr 130 135 140

Glu Gly Arg Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Arg Ser Lys
145 150 155 160

Tyr Gly Met Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp Trp Val 165 170 175

Tyr Tyr Glu Ser Lys Ala His Ile His Cys Ser Val Lys Ala Glu Asn 180 185 190

Ser Val Ala Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Ala Thr Val 195 200 205

His Leu Glu His Gly Gly Thr Lys Leu Val Lys Asp Leu Ser Pro Gly 210 215 220

Asp Arg Val Leu Ala Ala Asp Ala Asp Gly Arg Leu Leu Tyr Ser Asp 225 230 235 240

Phe Leu Thr Phe Leu Asp Arg Met Asp Ser Ser Arg Lys Leu Phe Tyr 245 250 255

Val Ile Glu Thr Arg Gln Pro Arg Ala Arg Leu Leu Leu Thr Ala Ala 260 265. 270

His Leu Leu Phe Val Ala Pro Gln His Asn Gln Ser Glu Ala Thr Gly 275 280 285

Ser Thr Ser Gly Gln Ala Leu Phe Ala Ser Asn Val Lys Pro Gly Gln 290 295 300

Arg Val Tyr Val Leu Gly Glu Gly Gln Gln Leu Leu Pro Ala Ser 305 310 315

Val His Ser Val Ser Leu Arg Glu Glu Ala Ser Gly Ala Tyr Ala Pro 325 330 335

Leu Thr Ala Gln Gly Thr Ile Leu Ile Asn Arg Val Leu Ala Ser Cys 340 345 350

Tyr Ala Val Ile Glu Glu His Ser Trp Ala His Trp Ala Phe Ala Pro 355 360 365

Phe Arg Leu Ala Gln Gly Leu Leu Ala Ala Leu Cys Pro Asp Gly Ala 370 375 380

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Val Pro Ser Met Pro Glu Arg Thr Leu Gly Ala Ser Gly Pro Ala Glu 50 60

Gly Arg Val Thr Arg Gly Ser Glu Arg Phe Arg Asp Leu Val Pro Asn 65 70 75 80

Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Ser Gly Ala Asp 85 90 95

Arg Leu Met Thr Glu Arg Cys Lys Glu Arg Val Asn Ala Leu Ala Ile 100 105 110 Ala Val Met Asn Met Trp Pro Gly Val Arg Leu Arg Val Thr Glu Gly
115 120 125

Trp Asp Glu Asp Gly His His Ala Gln Asp Ser Leu His Tyr Glu Gly 130 135 140

Arg Ala Leu Asp Ile Thr Thr Ser Asp Arg Asp Arg Asn Lys Tyr Gly
145 150 155 160

Leu Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp Trp Val Tyr Tyr
165 170 175

Glu Ser Arg Asn His Ile His Val Ser Val Lys Ala Asp Asn Ser Leu 180 185 190

Ala Val Arg Ala Gly Gly Cys Phe Pro Gly Asn Ala Thr Val Arg Leu 195 200 205

Arg Ser Gly Glu Arg Lys Gly Leu Arg Glu Leu His Arg Gly Asp Trp 210 215 220

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Leu Phe Leu Asp Arg Asp Leu Gln Arg Arg Ala Ser Phe Val Ala Val
245 250 255

Glu Thr Glu Arg Pro Pro Arg Lys Leu Leu Leu Thr Pro Trp His Leu 260 265 270

Val Phe Ala Ala Arg Gly Pro Ala Pro Ala Pro Gly Asp Phe Ala Pro 275 280 . 285

Val Phe Ala Arg Arg Leu Arg Ala Gly Asp Ser Val Leu Ala Pro Gly 290 295 300

Gly Asp Ala Leu Gln Pro Ala Arg Val Ala Arg Val Ala Arg Glu Glu 305 310 315 320

Ala Val Gly Val Phe Ala Pro Leu Thr Ala His Gly Thr Leu Leu Val 325 330 335

Asn Asp Val Leu Ala Ser Cys Tyr Ala Val Leu Glu Ser His Gln Trp 340 345 350

Ala His Arg Ala Phe Ala Pro Leu Arg Leu Leu His Ala Leu Gly Ala 355 360 365

Leu Leu Pro Gly Gly Ala Val Gln Pro Thr Gly Met His Trp Tyr Ser 370 380

Arg Leu Leu Tyr Arg Leu Ala Glu Glu Leu Met Gly 385 390 395

<210> 12 <211> 411 <212> PRT

<213> murine Ihh

<400> 12

Met Ser Pro Ala Trp Leu Arg Pro Arg Leu Arg Phe Cys Leu Phe Leu 1 5 10 15

Leu Leu Leu Leu Val Pro Ala Ala Arg Gly Cys Gly Pro Gly Arg
20 25 30

Val Val Gly Ser Arg Arg Arg Pro Pro Arg Lys Leu Val Pro Leu Ala 35 40 45

Tyr Lys Gln Phe Ser Pro Asn Val Pro Glu Lys Thr Leu Gly Ala Ser 50 55 60

Gly Arg Tyr Glu Gly Lys Ile Ala Arg Ser Ser Glu Arg Phe Lys Glu 65 70 75 80

Leu Thr Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn
85 90 95

Thr Gly Ala Asp Arg Leu Met Thr Gln Arg Cys Lys Asp Arg Leu Asn 100 105 110

Ser Leu Ala Ile Ser Val Met Asn Gln Trp Pro Gly Val Lys Leu Arg 115 120 125

Val Thr Glu Gly Arg Asp Glu Asp Gly His His Ser Glu Glu Ser Leu 130 135 140

His Tyr Glu Gly Arg Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Arg 145 150 155 160

Asn Lys Tyr Gly Leu Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp 165 170 175

Trp Val Tyr Tyr Glu Ser Lys Ala His Val His Cys Ser Val Lys Ser 180 185 190

Glu His Ser Ala Ala Ala Lys Thr Gly Gly Cys Phe Pro Ala Gly Ala 195 200 205

Gln Val Arg Leu Glu Asn Gly Glu Arg Val Ala Leu Ser Ala Val Lys 210 215 220

Pro Gly Asp Arg Val Leu Ala Met Gly Glu Asp Gly Thr Pro Thr Phe 225 230 235 240

Ser Asp Val Leu Ile Phe Leu Asp Arg Glu Pro Asn Arg Leu Arg Ala 245 250 255

Phe Gln Val Ile Glu Thr Gln Asp Pro Pro Arg Arg Leu Ala Leu Thr 260 265 270

Pro Ala His Leu Leu Phe Ile Ala Asp Asn His Thr Glu Pro Ala Ala 275 280 285 His Phe Arg Ala Thr Phe Ala Ser His Val Gln Pro Gly Gln Tyr Val 290 295 300

Leu Val Ser Gly Val Pro Gly Leu Gln Pro Ala Arg Val Ala Ala Val 305 310 315 320

Ser Thr His Val Ala Leu Gly Ser Tyr Ala Pro Leu Thr Arg His Gly 325 330 335

Thr Leu Val Val Glu Asp Val Val Ala Ser Cys Phe Ala Ala Val Ala 340 345 350

Asp His His Leu Ala Gln Leu Ala Phe Trp Pro Leu Arg Leu Phe Pro 355 360 365

Ser Leu Ala Trp Gly Ser Trp Thr Pro Ser Glu Gly Val His Ser Tyr 370 375 380

Pro Gln Met Leu Tyr Arg Leu Gly Arg Leu Leu Glu Glu Ser Thr 385 390 395 400

Phe His Pro Leu Gly Met Ser Gly Ala Gly Ser 405 410

<210> 13

<211> 437

<212> PRT

<213> murine Shh

<400> 13

Met Leu Leu Leu Leu Ala Arg Cys Phe Leu Val Ile Leu Ala Ser Ser 1 5 10 15

Leu Leu Val Cys Pro Gly Leu Ala Cys Gly Pro Gly Arg Gly Phe Gly
20 25 30

Lys Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys Gln Phe 35 40 45

Ile Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Arg Tyr Glu
50 60

Gly Lys Ile Thr Arg Asn Ser Glu Arg Phe Lys Glu Leu Thr Pro Asn 65 70 75 80

Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Gly Ala Asp 85 90 95

Arg Leu Met Thr Gln Arg Cys Lys Asp Lys Leu Asn Ala Leu Ala Ile 100 \$105\$ 110

Ser Val Met Asn Gln Trp Pro Gly Val Arg Leu Arg Val Thr Glu Gly
115 120 125

Trp Asp Glu Asp Gly His His Ser Glu Glu Ser Leu His Tyr Glu Gly 130 135 140

Arg Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Arg Ser Lys Tyr Gly
145 150 155 160

Met Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp Trp Val Tyr Tyr 165 170 175

Glu Ser Lys Ala His Ile His Cys Ser Val Lys Ala Glu As
n Ser Val 180 185 190

Ala Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Ala Thr Val His Leu 195 200 205

Glu Gln Gly Gly Thr Lys Leu Val Lys Asp Leu Arg Pro Gly Asp Arg 210 215 220

Val Leu Ala Ala Asp Asp Gln Gly Arg Leu Leu Tyr Ser Asp Phe Leu 225 230 . 235 240

Thr Phe Leu Asp Arg Asp Glu Gly Ala Lys Lys Val Phe Tyr Val Ile
245 250 255

Glu Thr Leu Glu Pro Arg Glu Arg Leu Leu Leu Thr Ala Ala His Leu $\underline{260}$ $\underline{265}$ $\underline{270}$

Leu Phe Val Ala Pro His Asn Asp Ser Gly Pro Thr Pro Gly Pro Ser 275 280 285

Ala Leu Phe Ala Ser Arg Val Arg Pro Gly Gln Arg Val Tyr Val Val 290 295 300

Ala Glu Arg Gly Gly Asp Arg Arg Leu Leu Pro Ala Ala Val His Ser 305 310 315 320

Val Thr Leu Arg Glu Glu Glu Ala Gly Ala Tyr Ala Pro Leu Thr Ala 325 330 335

His Gly Thr Ile Leu Ile Asn Arg Val Leu Ala Ser Cys Tyr Ala Val 340 345 350

Ile Glu Glu His Ser Trp Ala His Arg Ala Phe Ala Pro Phe Arg Leu 355 360 365

Ala His Ala Leu Leu Ala Ala Leu Ala Pro Ala Arg Thr Asp Gly Gly 370 375 380

Gly Gly Ser Ile Pro Ala Ala Gln Ser Ala Thr Glu Ala Arg Gly 385 390 395 400

Ala Glu Pro Thr Ala Gly Ile His Trp Tyr Ser Gln Leu Leu Tyr His
405 410 415

Ile Gly Thr Trp Leu Leu Asp Ser Glu Thr Met His Pro Leu Gly Met 420 425 430

Ala Val Lys Ser Ser 435 <210> 14

<211> 418

<212> PRT

<213> zebrafish Shh

<400> 14

Met Arg Leu Leu Thr Arg Val Leu Leu Val Ser Leu Leu Thr Leu Ser 1 5 10 15

Leu Val Val Ser Gly Leu Ala Cys Gly Pro Gly Arg Gly Tyr Gly Arg
20 25 30

Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys Gln Phe Ile 35 40 45

Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Arg Tyr Glu Gly 50 55 60

Lys Ile Thr Arg Asn Ser Glu Arg Phe Lys Glu Leu Thr Pro Asn Tyr 65 70 75 80

Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Gly Ala Asp Arg 85 90 95

Leu Met Thr Gln Arg Cys Lys Asp Lys Leu Asn Ser Leu Ala Ile Ser 100 105 110

Val Met Asn His Trp Pro Gly Val Lys Leu Arg Val Thr Glu Gly Trp 115 120 125

Asp Glu Asp Gly His His Phe Glu Glu Ser Leu His Tyr Glu Gly Arg 130 135 140

Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Lys Ser Lys Tyr Gly Thr 145 150 155 160

Leu Ser Arg Leu Ala Val Glu Ala Gly Phe Asp Trp Val Tyr Tyr Glu 165 170 175

Ser Lys Ala His Ile His Cys Ser Val Lys Ala Glu Asn Ser Val Ala 180 185 190

Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Ala Leu Val Ser Leu Gln
195 200 205

Asp Gly Gln Lys Ala Val Lys Asp Leu Asn Pro Gly Asp Lys Val 210 215 220

Leu Ala Ala Asp Ser Ala Gly Asn Leu Val Phe Ser Asp Phe Ile Met 225 230 235 240

Phe Thr Asp Arg Asp Ser Thr Thr Arg Arg Val Phe Tyr Val Ile Glu 245 250 255

Thr Gln Glu Pro Val Glu Lys Ile Thr Leu Thr Ala Ala His Leu Leu 260 265 270

Phe Val Leu Asp Asn Ser Thr Glu Asp Leu His Thr Met Thr Ala Ala 275 280 285

Tyr Ala Ser Ser Val Arg Ala Gly Gln Lys Val Met Val Val Asp Asp 290 295 300

Ser Gly Gln Leu Lys Ser Val Ile Val Gln Arg Ile Tyr Thr Glu Glu 305 310 315 320

Gln Arg Gly Ser Phe Ala Pro Val Thr Ala His Gly Thr Ile Val Val 325 330 335

Asp Arg Ile Leu Ala Ser Cys Tyr Ala Val Ile Glu Asp Gln Gly Leu 340 345 350

Ala His Leu Ala Phe Ala Pro Ala Arg Leu Tyr Tyr Tyr Val Ser Ser 355 360 365

Phe Leu Ser Pro Lys Thr Pro Ala Val Gly Pro Met Arg Leu Tyr Asn 370 380

 $\frac{\text{Arg}}{385}$ Arg Gly Ser Thr $\frac{\text{Gly}}{390}$ Thr Pro Gly Ser $\frac{\text{Cys}}{395}$ His $\frac{\text{Gln}}{400}$ Met Gly Thr 400

Trp Leu Leu Asp Ser Asn Met Leu His Pro Leu Gly Met Ser Val Asn 405 410 415

Ser Ser

<210> 15

<211> 475

<212> PRT

<213> Homo sapien Shh

<220>

<223> Xaa at position 463 is any or unknown amino acid

<400> 15

Met Leu Leu Leu Ala Arg Cys Leu Leu Leu Val Leu Val Ser Ser Leu
1 5 10 15

Leu Val Cys Ser Gly Leu Ala Cys Gly Pro Gly Arg Gly Phe Gly Lys
20 25 30

Arg Arg His Pro Lys Lys Leu Thr Pro Leu Ala Tyr Lys Gln Phe Ile 35 40 45

Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Arg Tyr Glu Gly 50 55 60

Lys Ile Ser Arg Asn Ser Glu Arg Phe Lys Glu Leu Thr Pro Asn Tyr 65 70 75 80

Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Gly Ala Asp Arg 85 90 95

- Leu Met Thr Gln Arg Cys Lys Asp Lys Leu Asn Ala Leu Ala Ile Ser 100 105 110
- Val Met Asn Gln Trp Pro Gly Val Lys Leu Arg Val Thr Glu Gly Trp 115 120 125
- Asp Glu Asp Gly His His Ser Glu Glu Ser Leu His Tyr Glu Gly Arg 130 135 140
- Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Arg Ser Lys Tyr Gly Met 145 150 155 160
- Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp Trp Val Tyr Tyr Glu 165 170 175
- Ser Lys Ala His Ile His Cys Ser Val Lys Ala Glu Asn Ser Val Ala 180 185 190
- Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Ala Thr Val His Leu Glu
 195 200 205
- Gln Gly Gly Thr Lys Leu Val Lys Asp Leu Ser Pro Gly Asp Arg Val 210 215 . 220
- Leu Ala Ala Asp Asp Gln Gly Arg Leu Leu Tyr Ser Asp Phe Leu Thr 225 230 235 240
- Phe Leu Asp Arg Asp Asp Gly Ala Lys Lys Val Phe Tyr Val Ile Glu 245 250 255
- Thr Arg Glu Pro Arg Glu Arg Leu Leu Leu Thr Ala Ala His Leu Leu 260 265 270
- Phe Val Ala Pro His Asn Asp Ser Ala Thr Gly Glu Pro Glu Ala Ser 275 280 285
- Ser Gly Ser Gly Pro Pro Ser Gly Gly Ala Leu Gly Pro Arg Ala Leu 290 . 295 300
- Phe Ala Ser Arg Val Arg Pro Gly Gln Arg Val Tyr Val Val Ala Glu 305 310 315 320
- Arg Asp Gly Asp Arg Arg Leu Leu Pro Ala Ala Val His Ser Val Thr 325 330 335
- Leu Ser Glu Glu Ala Ala Gly Ala Tyr Ala Pro Leu Thr Ala Gln Gly 340 345 350
- Thr Ile Leu Ile Asn Arg Val Leu Ala Ser Cys Tyr Ala Val Ile Glu 355 360 365
- Glu His Ser Trp Ala His Arg Ala Phe Ala Pro Phe Arg Leu Ala His 370 380
- Ala Leu Leu Ala Ala Leu Ala Pro Ala Arg Thr Asp Arg Gly Gly Asp 385 390 395 400

Ser Gly Gly Gly Asp Arg Gly Gly Gly Gly Gly Arg Val Ala Leu Thr 405 410 415

Ala Pro Gly Ala Ala Asp Ala Pro Gly Ala Gly Ala Thr Ala Gly Ile 420 425 430

His Trp Tyr Ser Gln Leu Leu Tyr Gln Ile Gly Thr Trp Leu Leu Asp 435 440 445

Ser Glu Ala Leu His Pro Leu Gly Met Ala Val Lys Ser Ser Xaa Ser 450 455 460

Arg Gly Ala Gly Gly Gly Ala Arg Glu Gly Ala 465 470 475

<210> 16

<211> 411

<212> PRT

<213> Homo sapien Ihh

<400> 16

Met Ser Pro Ala Arg Leu Arg Pro Arg Leu His Phe Cys Leu Val Leu 1 5 10 15

Leu Leu Leu Val Val Pro Ala Ala Trp Gly Cys Gly Pro Gly Arg
20 25 30

Val Val Gly Ser Arg Arg Pro Pro Arg Lys Leu Val Pro Leu Ala 35 40 45

Tyr Lys Gln Phe Ser Pro Asn Val Pro Glu Lys Thr Leu Gly Ala Ser 50 55 60

Gly Arg Tyr Glu Gly Lys Ile Ala Arg Ser Ser Glu Arg Phe Lys Glu 65 70 75 80

Leu Thr Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn 85 90 95

Thr Gly Ala Asp Arg Leu Met Thr Gln Arg Cys Lys Asp Arg Leu Asn 100 105 110

Ser Leu Ala Ile Ser Val Met Asn Gln Trp Pro Gly Val Lys Leu Arg 115 120 125

Val Thr Glu Gly Trp Asp Glu Asp Gly His His Ser Glu Glu Ser Leu 130 135 140

His Tyr Glu Gly Arg Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Arg 145 150 155 160

Asn Lys Tyr Gly Leu Leu Ala Arg Leu Ala Val Glu Ala Gly Phe Asp 165 170 175

Trp Val Tyr Tyr Glu Ser Lys Ala His Val His Cys Ser Val Lys Ser 180 185 190 Glu His Ser Ala Ala Ala Lys Thr Gly Gly Cys Phe Pro Ala Gly Ala 195 200 205

Gln Val Arg Leu Glu Ser Gly Ala Arg Val Ala Leu Ser Ala Val Arg 210 215 220

Pro Gly Asp Arg Val Leu Ala Met Gly Glu Asp Gly Ser Pro Thr Phe 225 230 235 240

Ser Asp Val Leu Ile Phe Leu Asp Arg Glu Pro His Arg Leu Arg Ala 245 250 255

Phe Gln Val Ile Glu Thr Gln Asp Pro Pro Arg Arg Leu Ala Leu Thr 260 265 270

Pro Ala His Leu Leu Phe Thr Ala Asp Asn His Thr Glu Pro Ala Ala 275 280 285

Arg Phe Arg Ala Thr Phe Ala Ser His Val Gln Pro Gly Gln Tyr Val 290 295 300

Leu Val Ala Gly Val Pro Gly Leu Gln Pro Ala Arg Val Ala Ala Val 305 310 315 320

Ser Thr His Val Ala Leu Gly Ala Tyr Ala Pro Leu Thr Lys His Gly 325 330 335

Thr Leu Val Val Glu Asp Val Val Ala Ser Cys Phe Ala Ala Val Ala 340 345 350

Asp His His Leu Ala Gln Leu Ala Phe Trp Pro Leu Arg Leu Phe His 355 360 365

Ser Leu Ala Trp Gly Ser Trp Thr Pro Gly Glu Gly Val His Trp Tyr 370 375 380

Pro Gln Leu Leu Tyr Arg Leu Gly Arg Leu Leu Leu Glu Glu Gly Ser 385 390 395 400

Phe His Pro Leu Gly Met Ser Gly Ala Gly Ser 405 410

<210> 17

<211> 416

<212> PRT

<213> Zebrafish Thh

<400> 17

Met Asp Val Arg Leu His Leu Lys Gln Phe Ala Leu Leu Cys Phe Ile 1 5 10 15

Ser Leu Leu Thr Pro Cys Gly Leu Ala Cys Gly Pro Gly Arg Gly 20 25 30

Tyr Gly Lys Arg Arg His Pro Lys Leu Thr Pro Leu Ala Tyr Lys
35 40 45

Gln Phe Ile Pro Asn Val Ala Glu Lys Thr Leu Gly Ala Ser Gly Lys 50 55 60

Tyr Glu Gly Lys Ile Thr Arg Asn Ser Glu Arg Phe Lys Glu Leu Ile 65 70 75 80

Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys Asp Glu Glu Asn Thr Asn 85 90 95

Ala Asp Arg Leu Met Thr Lys Arg Cys Lys Asp Lys Leu Asn Ser Leu 100 105 110

Ala Ile Ser Val Met Asn His Trp Pro Gly Val Lys Leu Arg Val Thr
115 120 125

Glu Gly Trp Asp Glu Asp Gly His His Leu Glu Glu Ser Leu His Tyr 130 135 140

Glu Gly Arg Ala Val Asp Ile Thr Thr Ser Asp Arg Asp Lys Ser Lys 145 150 155 160

Tyr Gly Met Leu <u>Ser Arg</u> Leu Ala <u>Val Glu Ala Gly Phe Asp Trp Val</u>
165 170 175

Tyr Tyr Glu Ser Lys Ala His Ile His Cys Ser Val Lys Ala Glu Asn 180 185 190

Ser Val Ala Ala Lys Ser Gly Gly Cys Phe Pro Gly Ser Gly Thr Val

Thr Leu Gly Asp Gly Thr Arg Lys Pro Ile Lys Asp Leu Lys Val Gly 210 215 220

Asp Arg Val Leu Ala Ala Asp Glu Lys Gly Asn Val Leu Ile Ser Asp 225 230 235 240

Phe Ile Met Phe Ile Asp His Asp Pro Thr Thr Arg Arg Gln Phe Ile 245 250 255

Val Ile Glu Thr Ser Glu Pro Phe Thr Lys Leu Thr Leu Thr Ala Ala 260 265 270

His Leu Val Phe Val Gly Asn Ser Ser Ala Ala Ser Gly Ile Thr Ala 275 280 285

Thr Phe Ala Ser Asn Val Lys Pro Gly Asp Thr Val Leu Val Trp Glu 290 295 300

Asp Thr Cys Glu Ser Leu Lys Ser Val Thr Val Lys Arg Ile Tyr Thr 305 310 315 320

Glu Glu His Glu Gly Ser Phe Ala Pro Val Thr Ala His Gly Thr Ile 325 330 335

Ile Val Asp Gln Val Leu Ala Ser Cys Tyr Ala Val Ile Glu Asn His 340 345 350

Lys Trp Ala His Trp Ala Phe Ala Pro Val Arg Leu Cys His Lys Leu 355 360 365

Met Thr Trp Leu Phe Pro Ala Arg Glu Ser Asn Val Asn Phe Gln Glu 370 375 380

Asp Gly Ile His Trp Tyr Ser Asn Met Leu Phe His Ile Gly Ser Trp 385 390 395 400

Leu Leu Asp Arg Asp Ser Phe His Pro Leu Gly Ile Leu His Leu Ser 405 410 415

<210> 18

<211> 471

<212> PRT

<213> Drosophila HH

<400> 18

Met Asp Asn His Ser Ser Val Pro Trp Ala Ser Ala Ala Ser Val Thr 1 5 10 15

Cys Leu Ser Leu Gly Cys Gln Met Pro Gln Phe Gln Phe Gln Phe Gln 20 25 30

Leu Gln Ile Arg Ser Glu Leu His Leu Arg Lys Pro Ala Arg Arg Thr
35 40 45

Gln Thr Met Arg His Ile Ala His Thr Gln Arg Cys Leu Ser Arg Leu 50 55 60

Thr Ser Leu Val Ala Leu Leu Leu Ile Val Leu Pro Met Val Phe Ser 65 70 75 80

Pro Ala His Ser Cys Gly Pro Gly Arg Gly Leu Gly Arg His Arg Ala 85 90 95

Arg Asn Leu Tyr Pro Leu Val Leu Lys Gln Thr Ile Pro Asn Leu Ser 100 105 110

Glu Tyr Thr Asn Ser Ala Ser Gly Pro Leu Glu Gly Val Ile Arg Arg 115 120 125

Asp Ser Pro Lys Phe Lys Asp Leu Val Pro Asn Tyr Asn Arg Asp Ile 130 135 140

Leu Phe Arg Asp Glu Glu Gly Thr Gly Ala Asp Gly Leu Met Ser Lys
145 150 155 160

Arg Cys Lys Glu Lys Leu Asn Val Leu Ala Tyr Ser Val Met Asn Glu 165 170 175

Trp Pro Gly Ile Arg Leu Leu Val Thr Glu Ser Trp Asp Glu Asp Tyr 180 185 190

His His Gly Gln Glu Ser Leu His Tyr Glu Gly Arg Ala Val Thr Ile 195 200 205 Ala Thr Ser Asp Arg Asp Gln Ser Lys Tyr Gly Met Leu Ala Arg Leu 210 215 220

Ala Val Glu Ala Gly Phe Asp Trp Val Ser Tyr Val Ser Arg Arg His 225 230 235 240

Ile Tyr Cys Ser Val Lys Ser Asp Ser Ser Ile Ser Ser His Val His 245 250 255

Gly Cys Phe Thr Pro Glu Ser Thr Ala Leu Leu Glu Ser Gly Val Arg
260 265 270

Lys Pro Leu Gly Glu Leu Ser Ile Gly Asp Arg Val Leu Ser Met Thr 275 280 285

Ala Asn Gly Gln Ala Val Tyr Ser Glu Val Ile Leu Phe Met Asp Arg 290 295 300

Asn Leu Glu Gln Met Gln Asn Phe Val Gln Leu His Thr Asp Gly Gly 305 310 315 320

Ala Val Leu Thr Val Thr Pro Ala His Leu Val Ser Val Trp Gln Pro 325 330 335

Glu Ser Gln Lys Leu Thr Phe Val Phe Ala His Arg Ile Glu Glu Lys 340 345 350

Asn Gln Val Leu Val Arg Asp Val Glu Thr Gly Glu Leu Arg Pro Gln 355 360 365

Arg Val Val Lys Leu Gly Ser Val Arg Ser Lys Gly Val Val Ala Pro 370 380

Leu Thr Arg Glu Gly Thr Ile Val Val Asn Ser Val Ala Ala Ser Cys 385 390 395 400

Tyr Ala Val Ile Asn Ser Gln Ser Leu Ala His Trp Gly Leu Ala Pro 405 410 415

Met Arg Leu Leu Ser Thr Leu Glu Ala Trp Leu Pro Ala Lys Glu Gln
420 425 430

Leu His Ser Ser Pro Lys Val Val Ser Ser Ala Gln Gln Gln Asn Gly
435 440 445

Ile His Trp Tyr Ala Asn Ala Leu Tyr Lys Val Lys Asp Tyr Val Leu 450 455 460

Pro Gln Ser Trp Arg His Asp 465 470

<210> 19

<211> 221

<212> PRT

<213> Artificial Sequence

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<220>
<223> Description of Artificial Sequence: degenerate
      polypeptide sequence
<220>
<222> 7
<223> Gly, Ala, Val, Leu, Ile, Phe, Tyr or Trp
<220>
<222> 9
<223> Arg, His or Lys
<220>
<222> 44
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 85
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 93
<223> Lys, Arg, His, Asn or Gln
<220>
<222> 98
<223> Lys, Arg or His
<220>
<222> 112
<223> Ser, Thr, Tyr, Trp or Phe
<220>
<222> 132
<223> Lys, Arg or His
<220>
<222> 137
<223> Met, Cys, Ser or Thr
<220>
<222> 139
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 181
<223> Leu, Val, Met, Thr or Ser
<220>
<222> 183
<223> His, Phe, Tyr, Ser, Thr, Met or Cys
<220>
<222> 185
<223> Gln, Asn, Glu, or Asp
<220>
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<222> 186
<223> His, Phe, Tyr, Thr, Gln, Asn, Glu or Asp
<220>
<222> 189
<223> Gln, Asn, Glu, Asp, Thr, Ser, Met or Cys
<220>
<222> 191
<223> Ala, Gly, Cys, Leu, Val or Met
<220>
<222> 196
<223> Arg, Lys, Met, Ile, Asn, Asp, Glu, Gln, Ser, Thr or Cys
<220>
<222> 200
<223> Arg, Lys, Met or Ile
<220>
<222> 206
<223> Ala, Gly, Cys, Asp, Glu, Gln, Asn, Ser, Thr or Met
<220>
<222> 207
<223> Ala, Gly, Cys, Asp, Asn, Glu or Gln
<220>
<222> 209
<223> Arg, Lys, Met, Ile, Asn, Asp, Glu or Gln
<220>
<222> 211
<223> Leu, Val, Met or Ile
<220>
<222> 212
<223> Phe, Tyr, Thr, His or Trp
<220>
<222> 216
<223> Ile, Val, Leu or Met
<220>
<223> Met, Cys, Ile, Leu, Val, Thr or Ser
<220>
<222> 219
<223> Leu, Val, Met, Thr or Ser
<220>
<223> each Xaa may also be any amino acid.
<400> 19
Cys Gly Pro Gly Arg Gly Xaa Gly Xaa Arg Arg His Pro Lys Lys Leu
                  5
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Thr Pro Leu Ala Tyr Lys Gln Phe Ile Pro Asn Val Ala Glu Lys Thr 20 25 30

Leu Gly Ala Ser Gly Arg Tyr Glu Gly Lys Ile Xaa Arg Asn Ser Glu 35 40 45

Arg Phe Lys Glu Leu Thr Pro Asn Tyr Asn Pro Asp Ile Ile Phe Lys 50 55 60

Asp Glu Glu Asn Thr Gly Ala Asp Arg Leu Met Thr Gln Arg Cys Lys 65 70 75 80

Asp Lys Leu Asn Xaa Leu Ala Ile Ser Val Met Asn Xaa Trp Pro Gly 85 90 95

Val Xaa Leu Arg Val Thr Glu Gly Trp Asp Glu Asp Gly His His Xaa 100 105 110

Glu Glu Ser Leu His Tyr Glu Gly Arg Ala Val Asp Ile Thr Thr Ser 115 120 125

Asp Arg Asp Xaa Ser Lys Tyr Gly Xaa Leu Xaa Arg Leu Ala Val Glu 130 135 140

Ala Gly Phe Asp Trp Val Tyr Tyr Glu Ser Lys Ala His Ile His Cys 145 150 155 160

Ser Val Lys Ala Glu Asn Ser Val Ala Ala Lys Ser Gly Gly Cys Phe 165 170 175

Pro Gly Ser Ala Xaa Val Xaa Leu Xaa Xaa Gly Gly Xaa Lys Xaa Val 180 185 190

Lys Asp Leu Xaa Pro Gly Asp Xaa Val Leu Ala Ala Asp Xaa Xaa Gly 195 200 205

Xaa Leu Xaa Xaa Ser Asp Phe Xaa Xaa Phe Xaa Asp Arg 210 215 220

<210> 20

<211> 167

<212> PRT

<213> Artificial Sequence

<220>

<223> Description of Artificial Sequence: degenerate
 polypeptide sequence

<220>

<222> 7

<223> Gly, Ala, Val, Leu, Ile, Pro, Phe or Tyr

<220>

<222> 8

<223> Gly, Ala, Val, Leu or Ile

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<220>
<222> 9
<223> Gly, Ala, Val, Leu, Ile, Lys, His or Arg
<220>
<222> 12
<223> Lys, Arg or His
<220>
<222> 13
<223> Phe, Trp, Tyr or an amino acid gap
<220>
<222> 14
<223> Gly, Ala, Val, Leu, Ile or an amino acid gap
<220>
<222> 17
<223> Asn, Gln, His, Arg or Lys
<220>
<222> 19
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 22
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 27
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 29
<223> Ser, Thr, Gln or Asn
<220>
<222> 30
<223> Met, Cys, Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 31
<223> Gly, Ala, Val, Leu, Ile or Pro
<220>
<222> 33
<223> Arg, His or Lys
<220>
<222> 40
<223> Gly, Ala, Val, Leu, Ile, Pro, Arg, His or Lys
<220>
<222> 41
<223> Gly, Ala, Val, Leu, Ile, Phe or Tyr
<220>
<222> 44
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<223> Arg, His or Lys
<220>
<222> 45
<223> Gly, Ala, Val, Leu, Ile, Ser or Thr
<220>
<222> 46
<223> Thr or Ser
<220>
<222> 48
<223> Gly, Ala, Val, Leu, Ile, Asn or Gln
<220>
<222> 53
<223> Arg, His or Lys
<220>
<222> 54
<223> Asp or Glu
<220>
<222> 71
<223> Ser or Thr
<220>
<222> 79
<223> Glu, Asp, Gln or Asn
<220>
<222> 83
<223> Glu or Asp
<220>
<222> 84
<223> Arg, His or Lys
<220>
<222> 85
<223> Gly, Ala, Val, Leu or Ile
<220>
<222> 87
<223> Gly, Ala, Val, Leu, Ile, Thr or Ser
<220>
<222> 95
<223> Met, Cys, Gln, Asn, Arg, Lys or His
<220>
<222> 100
<223> Arg, His or Lys
<220>
<222> 107
<223> Trp, Phe, Tyr, Arg, His or Lys
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<220>
<222> 114
<223> Gly, Ala, Val, Leu, Ile, Ser, Thr, Tyr or Phe
<220>
<222> 115
<223> Gln, Asn, Asp or Glu
<220>
<222> 116
<223> Asp or Glu
<220>
<222> 125
<223> Gly, Ala, Val, Leu, or Ile
<220>
<222> 134
<223> Arg, His or Lys
<220>
<222> 135
<223> Asn, Gln, Thr or Ser
<220>
<222> 139
<223> Gly, Ala, Val, Leu, Ile, Ser, Thr, Met or Cys
<220>
<222> 141
<223> Gly, Ala, Val, Leu, Ile, Thr or Ser
<220>
<222> 157
<223> Arg, His or Lys
<220>
<222> 158
<223> Asn, Gln, Gly, Ala, Val, Leu or Ile
<220>
<222> 160
<223> Gly, Ala, Val, Leu or Ile
<220>
<222> 162
<223> Gly, Ala, Val, Leu, Ile, Ser, Thr or Cys
<220>
<222> 166
<223> Gly, Ala, Val, Leu, Ile, Thr or Ser
<220>
<222> 167
<223> Asp or Glu
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<400> 20
Cys Gly Pro Gly Arg Gly Xaa Xaa Xaa Arg Arg Xaa Xaa Yaa Pro Lys
Xaa Leu Xaa Pro Leu Xaa Tyr Lys Gln Phe Xaa Pro Xaa Xaa Kaa Glu
Xaa Thr Leu Gly Ala Ser Gly Xaa Xaa Glu Gly Xaa Xaa Xaa Arg Xaa
Ser Glu Arg Phe Xaa Xaa Leu Thr Pro Asn Tyr Asn Pro Asp Ile Ile
Phe Lys Asp Glu Glu Asn Xaa Gly Ala Asp Arg Leu Met Thr Xaa Arg
                                         75
Cys Lys Xaa Xaa Xaa Asn Xaa Leu Ala Ile Ser Val Met Asn Xaa Trp
Pro Gly Val Xaa Leu Arg Val Thr Glu Gly Xaa Asp Glu Asp Gly His
His Xaa Xaa Xaa Ser Leu His Tyr Glu Gly Arg Ala Xaa Asp Ile Thr
                            120
Thr Ser Asp Arg Asp Xaa Xaa Lys Tyr Gly Xaa Leu Xaa Arg Leu Ala
Val Glu Ala Gly Phe Asp Trp Val Tyr Tyr Glu Ser Xaa Xaa His Xaa
His Xaa Ser Val Lys Xaa Xaa
<210> 21
<211> 74
<212> DNA
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